## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

M.L. Bayne et al.

Serial No.:

To be assigned

Case No. 18199CB

Filed:

Submitted on even date herewith

Examiner:

1646

For:

DNA MOLECULES ENCODING VASCULAR ENDOTHELIAL CELL GROWTH FACTOR II

CIPLINATED (A. A. a. a. d. d. Hansin)

L. Spector

SUBUNITS (As Amended Herein)

Assistant Commissioner of Patents Washington, D.C. 20231

# PRELIMINARY AMENDMENT, 37 C.F.R. §1.111, 1.115

Sir:

Preliminary to the examination of this Rule 53(b) continuation application, please calculate the filing fee due based on entry of new claims 22-37. Please enter the additional amendments and consider the following remarks. This application is copending to U.S. Application Serial No. 09/326,879, filed June 7, 1999. A Notice of Appeal was filed in the '879 application on September 10, 2001. A Petition to Extend Time under 37 C.F.R. §1.136(a) for three (3) months is entered on an even date herewith to continue pendency of the '879 application up to and including Monday, February 11, 2002. Applicants intend to cease further prosecution of the '879 case in favor of this above-identified continuation application.

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT FEMILIALY & 2002
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I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS
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AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER
FOR PATERTS, WASHINGTON, D.C., 20231.
DATE

## IN THE SPECIFICATION:

At page 1, line 2, please delete the title "VASCULAR ENDOTHELIAL CELL GROWTH FACTOR II" and insert a new title --DNA MOLECULES ENCODING VASCULAR ENDOTHELIAL CELL GROWTH FACTOR II SUBUNITS--.

At page 1, line 5, delete the continuing data and add the following continuing data:

-- This application is a continuation application of application no. 09/326,879, filed June 7, 1999, which is a divisional of application no. 09/038,199, filed March 10, 1998, issued as U.S. Patent No. 6,180,107, which is a divisional of application no. 08/299,185, filed August 31, 1994, issued as U.S. Patent No. 5,726,152, which is a continuation-in-part of application no. 08/000,834, filed January 5, 1993, abandoned, which is a continuation of application no. 07/586,638, filed September 21, 1990, abandoned. --.

At page 2, line 22, following "Figure 5", please insert -- and Figures 5A through 5C--.

At page 2, line 26, following "Figure 6", please insert -- and Figures 6A through 6B--.

At page 2, line 32 following "Figure 7", please insert -- and Figure 7A--.

At page 10, line 22, please delete "Figure 4" and insert -- Figures 4 through 4M--.

At page 11, line 5, please delete "Figure 4" and insert -- Figures 4 through 4M--.

At page 11, line 11, please delete "Fig. 4 and Fig. 5" and insert --Figures 4 through 4M and Figures 5 through 5C--.

At page 11, line 27, please delete "Figure 4" and insert -- Figures 4 through 4M--.

At page 11, line 33, please delete "Fig. 5 and Fig. 6" and insert --Figures 5 through 5C and Figures 6 through 6B--.

At page 12, line 5, please delete "Figs. 4 and 5" and insert --Figures 4 through 4M and Figures 5 through 5C--.

At page 13, line 3, please delete "Fig. 6 and Fig. 7" and insert --Figures 6 through 6B and Figures 7 through 7A--.

At page 23, line 15, please delete "Figs. 5 and 6" and insert -- -- Figures 5 through 5C and Figures 6 through 6B--.

At page 23, line 16, please delete "Fig. 5" and insert -- Figures 5 through 5C--.

At page 23, line 17, please delete "Fig. 6" and insert -- Figures 6 through 6B--.

At page 29, line 13, please delete "Fig. 5" and insert -- Figures 5 through 5C--.

At page 37, line 25 please delete "Figures 6 and 7" and insert --Figures 6 through 6B and Figures 7 through 7A--.

At page 39, line 31, please delete "Fig. 6 and Fig. 7" and insert --Figures 6 through 6B and Figures 7 through 7A--.

At page 39, line 33, please delete "Fig. 7" and insert -- Figures 7 through 7A--.

At page 40, line 1, please delete "Fig. 7" and insert -- Figures 7 through 7A--.

At page 42, line 20, please delete "Fig. 6" and insert -- Figures 6 through 6B--.

### IN THE CLAIMS:

Please cancel claims 1-21, without prejudice.

Please enter new claims 22-37, as follows:

- 22(New). A purified DNA molecule encoding a B subunit of vascular endothelial growth factor II wherein said B subunit comprises the 158 amino acid precursor protein as shown in Figure 6.
- 23(New). An expression vector for expressing a B subunit of vascular endothelial growth factor II in a recombinant host cell wherein said expression vector comprises a DNA molecule of claim 22.
- 24(New). A host cell which expresses a recombinant a B subunit of vascular endothelial growth factor II wherein said host cell contains the expression vector of claim 23.
- 25(New). A process for expressing a B subunit of vascular endothelial growth factor protein in a recombinant host cell, comprising:
- (a) transfecting the expression vector of claim 23 into a suitable host cell; and,
- (b) culturing the host cells of step (a) under conditions which allow expression of said B subunit of vascular endothelial growth factor protein from said expression vector.

- 26(New). A purified DNA molecule encoding a B subunit of vascular endothelial growth factor II wherein said B subunit comprises the 135 amino acid mature protein as shown in Figure 6.
- 27(New). An expression vector for expressing a B subunit of vascular endothelial growth factor II in a recombinant host cell wherein said expression vector comprises a DNA molecule of claim 26.
- 28(New). A host cell which expresses a recombinant a B subunit of vascular endothelial growth factor II wherein said host cell contains the expression vector of claim 27.
- 29(New). A process for expressing a B subunit of vascular endothelial growth factor protein in a recombinant host cell, comprising:
- (a) transfecting the expression vector of claim 27 into a suitable host cell; and,
- (b) culturing the host cells of step (a) under conditions which allow expression of said B subunit of vascular endothelial growth factor protein from said expression vector.
- 30(New). A purified DNA molecule encoding a B subunit of vascular endothelial growth factor II wherein said B subunit comprises the 138 amino acid precursor protein as shown in Figure 7.

- 31(New). An expression vector for expressing a B subunit of vascular endothelial growth factor  $\Pi$  in a recombinant host cell wherein said expression vector comprises a DNA molecule of claim 30.
- 32(New). A host cell which expresses a recombinant a B subunit of vascular endothelial growth factor II wherein said host cell contains the expression vector of claim 31.
- 33(New). A process for expressing a B subunit of vascular endothelial growth factor protein in a recombinant host cell, comprising:
- (a) transfecting the expression vector of claim 31 into a suitable host cell; and,
- (b) culturing the host cells of step (a) under conditions which allow expression of said B subunit of vascular endothelial growth factor protein from said expression vector.
- 34(New). A purified DNA molecule encoding a B subunit of vascular endothelial growth factor II wherein said B subunit comprises the 115 amino acid mature protein as shown in Figure 7.
- 35(New). An expression vector for expressing a B subunit of vascular endothelial growth factor II in a recombinant host cell wherein said expression vector comprises a DNA molecule of claim 34.
- 36(New). A host cell which expresses a recombinant a B subunit of vascular endothelial growth factor II wherein said host cell contains the expression vector of claim 35.

FI 1812 - 18

- 37(New). A process for expressing a B subunit of vascular endothelial growth factor protein in a recombinant host cell, comprising:
- (a) transfecting the expression vector of claim 35 into a suitable host cell; and,
- (b) culturing the host cells of step (a) under conditions which allow expression of said B subunit of vascular endothelial growth factor protein from said expression vector.

# REMARKS

Original claims 1-21 are cancelled, without prejudice.

New claims 22-37 are respectfully entered. New claims 22-37 correspond to allowed subject matter from U.S. Application Serial No. 09/326,879, as follows:

	%79 Application	New Claims
Claim#	26	22
	27	23
	28	24
	29	25
	30	26
	31	27
	32	28
	33	29
	34	30
	35	31
	36	32
	37	33
	38	34
	39	35
	40	36
	41	37

The specification was amended in anticipation of utilizing the same formal drawings as used in U.S. Patent No. 5,726,152, as well as updating the continuing data. Applicants respectfully note that reference should be made to appl. no. 07/586,638, not 07/586,631.

New claims 22-37 mirror allowed claims from the '879 application as noted above. Applicants reserve the right to pursue non-elected and/or non-recited subject matter in a future continuing application. No new matter is added by entry of new claims 22-37. Applicants respectfully take the position that the pending claims remain allowable. If necessary, the Examiner is invited to contact the undersigned attorney by telephone if clarification is required on any aspect of this response.

Respectfully submitted,

Bv

J. Mark Hand Reg. No.36,545

Attorney for Applicants

Merck & Co., Inc. P.O. Box 2000

Rahway, NJ 07065-0907

(732) 594-3905

Date: Franziski 8, 7002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

M. Bayne et al.

Art Unit:

1647

Serial No.:

09/326,879 - Case 18199CB

Examiner:

L. Spector

Filed:

Concurrently herewith (Express Mail EL523909946US)

For:

VASCULAR ENDOTHELIAL CELL GROWTH

**FACTOR II** 

Assistant Commissioner of Patents

Washington, D.C. 20231

#### **ATTENTION: Official Draftsman**

#### TRANSMITTAL OF FORMAL DRAWINGS

Sir:

Submitted herewith are new drawings to correct the informalities in the originally submitted drawings. Enclosed please find thirty two (32) sheets of formal drawings (Figs 1-11).

Should communication with the undersigned representative facilitate the review and the acceptance of the enclosed drawings, the Official Draftsman is invited to telephone the representative at the number listed below.

Respectfully submitted.

J. Mark Hand

Reg. No. 36,545

Attorney for Applicant MERCK & CO., INC.

P.O. Box 2000

Rahway, New Jersey 07065-0907

(732) 594-3905

(732) 594-4720 - fax

EXPRESS, MAIL CERTIFICATE

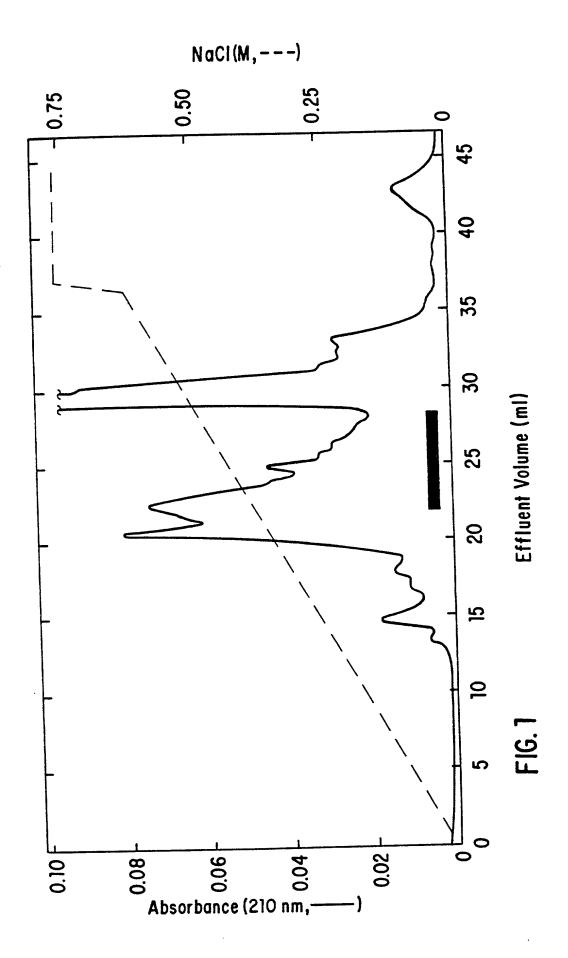
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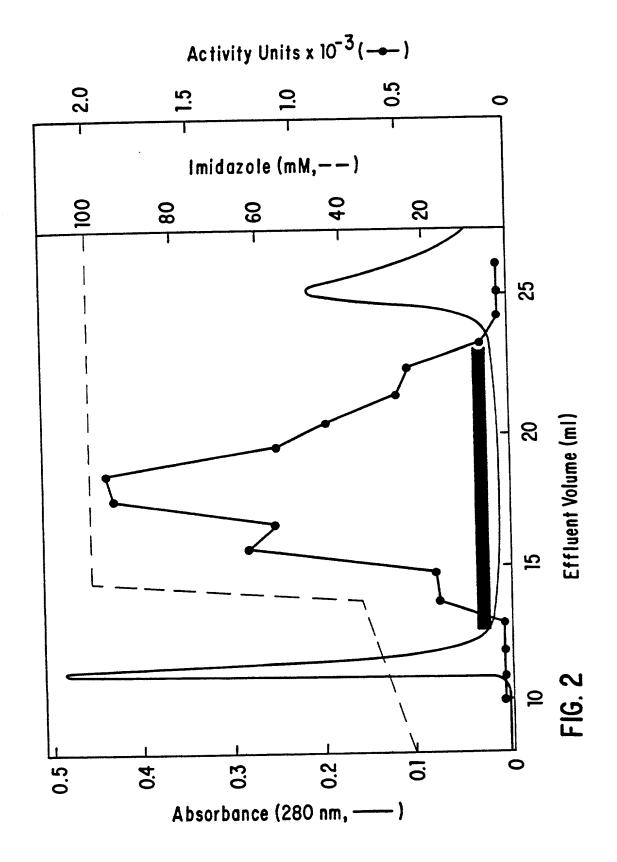
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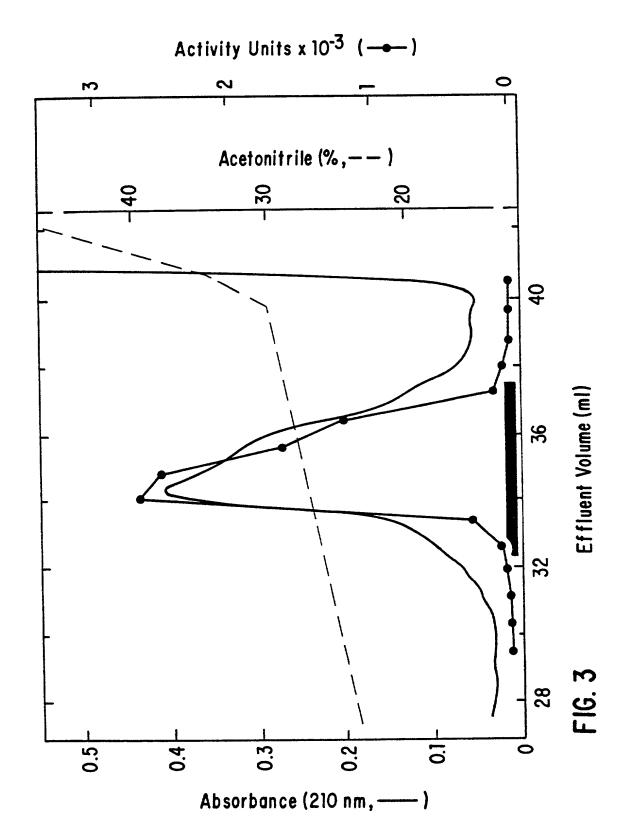
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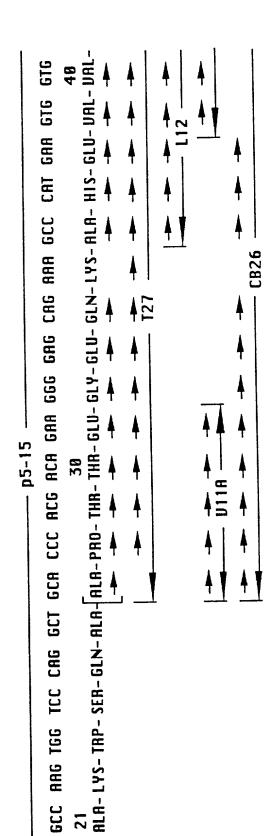
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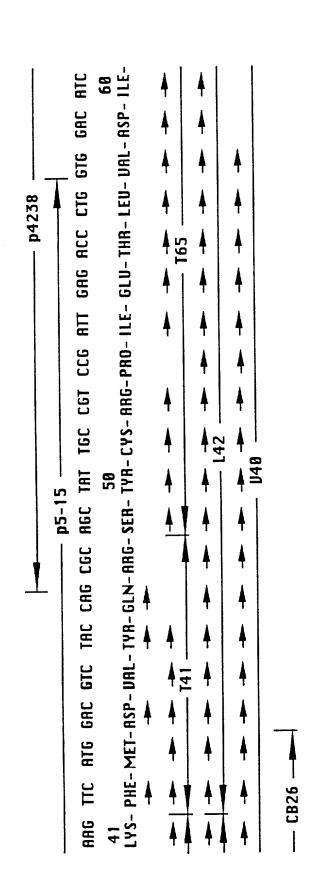




MET-ASN-PHE-LEU-LEU-SER-TRP-URL-HIS-TRP-THR-LEU-ALR-LEU-LEU-LEU-LEU-TYR-LEU-HIS-HIS-A ACC ATG AAC TTT CTG CTC TCT TGG GTG CAC TGG ACC CTG GCT TTA CTG CTG TAC CTC CAC CAT p5-15 ·

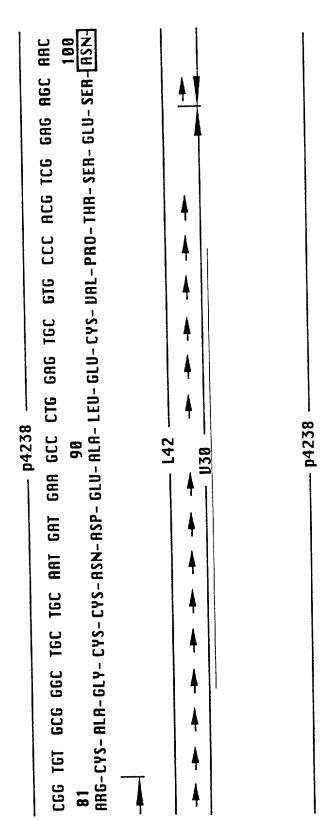


F16. 2



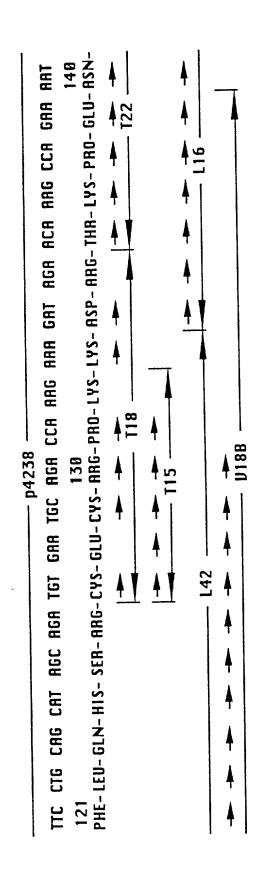
PHE-GLN-GLU-TYR-PRO-ASP-GLU-ILE-GLU-TYR-ILE-PHE-LYS-PRO-SER-CYS-UAL-PRO-LEU-MET-TTC CAG GAG TAC CCC GAT GAG ATA GAG TAT ATC TTC AAG CCG TCC TGT GTG CCC CTA ATG 130 **- 165** p4238

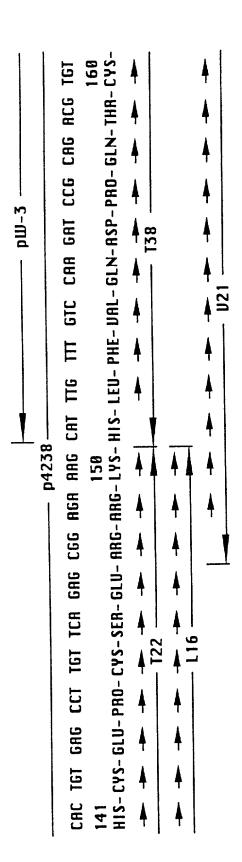
FIG. 4A



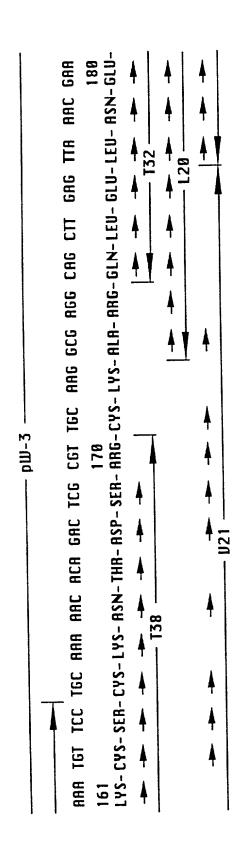
URL-THR-MET-GLN-ILE-MET-ARG-ILE-LYS-PRO-HIS-GLN-SER-GLN-HIS-ILE-GLY-GLU-MET-SER-120 GTC ACT ATG CAG ATC ATG CGG ATC AAA CCT CAC CAA AGC CAG CAC ATA GGA GAG ATG AGC CB18-19 -142**U18A** -

FIG. 4B





F16. 40



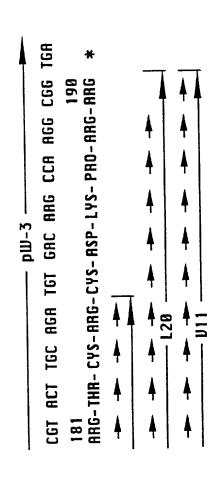
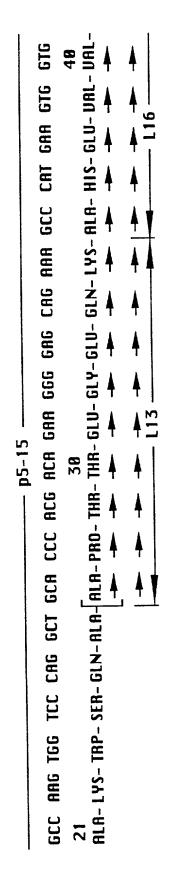
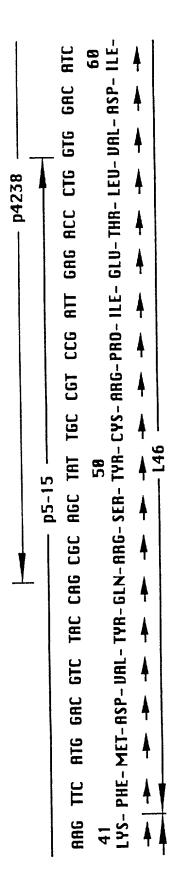


FIG. 4D

MET-ASN-PHE-LEU-LEU- SER- TRP-UAL- HIS- TRP-THR-LEU-ALA-LEU- LEU-LEU-LEU-TYR-LEU-HIS-HIS-20 CHT A ACC ATG AAC TIT CTG CTC TCT TGG GTG CAC TGG ACC CTG GCT TTA CTG CTG TAC CTC CAC - p5-15 -





F16. 4E

TTC CAG GAG TAC CCC GAT GAG ATA GAG TAT ATC TTC AAG CCG TCC TGT GTG CCC CTA ATG  78  88  PHE-GLN-GLU-TYR-PRO-ASP-GLU-ILE-GLU-TYR-ILE-PHE-LYS-PRO-SER-CYS-UAL-PRO-LEU-MET-  146	CGG TGT GCG GGC TGC RAT GAT GAA GCC CTG GAG TGC GTG CCC ACG TCG GAG AGC AAC 98  ARG-CYS-ALA-GLY-CYS-CYS-ASN-ASP-GLU-ALA-LEU-GLU-CYS-UAL-PRO-THA-SER-GLU-SER-RSN-ARG-CYS-ALA-CYS-CYS-ASN-ASP-GLU-ALA-LEU-GLU-CYS-UAL-PRO-THA-SER-GLU-SER-RSN-ARG-CYS-ALA-CYS-CYS-ASN-ASP-GLU-ALA-LEU-GLU-CYS-UAL-PRO-THA-SER-GLU-SER-RSN-ARG-CYS-ALA-CYS-CYS-ASN-ASP-GLU-ALA-LEU-GLU-CYS-UAL-PRO-THA-SER-GLU-SER-RSN-ARG-CYS-ALA-CYS-CYS-ASN-ASP-GLU-ALA-CYS-UAL-PRO-THA-SER-GLU-SER-RSN-ARG-CYS-ALA-CYS-CYS-ASN-ASP-GLU-ALA-CYS-UAL-PRO-THA-SER-GLU-SER-RSN-ASN-ASP-GLU-ALA-CYS-UAL-PRO-THA-SER-GLU-SER-RSN-ASP-GLU-ALA-CYS-UAL-PRO-THA-SER-GLU-CYS-UAL-PRO-THA-SER-GLU-CYS-ASN-ASP-GLU-ALA-CYS-UAL-PRO-THA-SER-GLU-CYS-UAL-PRO-THA-SER-GLU-CYS-UAL-PRO-THA-SER-GLU-CYS-UAL-PRO-THA-CYS-UAL-PRO-THA-CYS-UAL-PRO-THA-CYS-UAL-CYS-UAL-PRO-THA-CYS-UAL-CYS-UAL-PRO-THA-CYS-UAL-CYS-UAL-PRO-THA-CYS-UAL-CY	GTC RCT RTG CRG RTC RRR CCT CRC CRR RGC CRG CRC RTR GGR GRG RTG RGC 189  181  URL-THR-MET-GLN-ILE-MET-RRG-ILE-LYS-PRO-HIS-GLN-SER-GLN-HIS-ILE-GLY-GLU-MET-SER-
TTC CAL	CGG TGT 81 RRG-CY	GTC RCT 101 URL-THR-

FIG. 4F

FIG. 46

CGT RCT TGC RGR TGT GRC RRG CCR RGG CGG TGR
181
RRG-THR-CYS-RRG-CYS-RSP-LYS-PRO-RRG-RRG \*

F16. 4H

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od –		TH	EU- 1
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		<u>G</u>	Ja-
		CAG GTC CTA GCT	Z 19
		116	LEU-
		ΩL	18 PHE-
	2	TGC	CYS-
	- 282	ACT	THR-
		TTC RCT TGC TTC	PHE-
		CTG	· LEU-
		ARG CTG	-ShT-
		RTG	MET-
-		<b>339</b>	ALA-
		CTG	1 MET- LEU- ALA- MET-LYS- LEU- PHE-THR- CYS-PHE-LEU- GLN-UAL- LEU- ALA- GLY- LEU-
	1	ATG	MET-

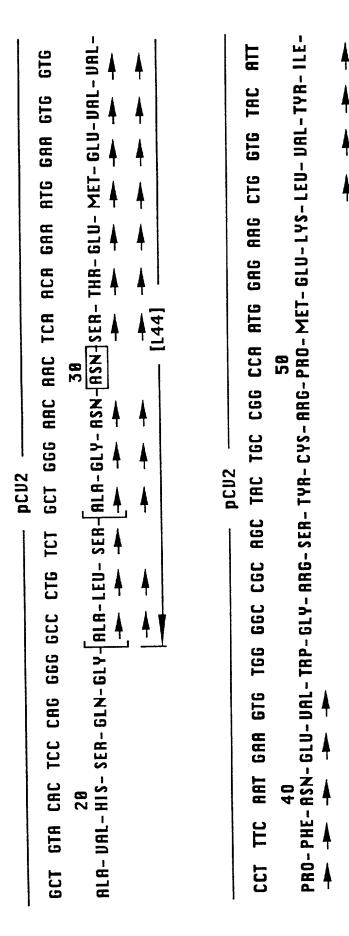


FIG. 4 I

[[44]

	AGT	SER-	<b>A</b>	BSN-	ATG	118 ILE- THR- MET-GLN- ILE- LEU- LYS- ILE- PRO-PRO-RSN-RRG- RSP-PRO-HIS- SER-TYR- URL-GLU- MET-	<b>A</b>
	CTG	70 LU- UAL-SER- HIS- ILE- PHE- SER-PRO- SER-CYS- UAL-LEU- LEU- SER-		6T GRC GRG GGT CTG CRC TGT GTG GCG CTR RRG RCR GCC RRC 98  LY-RSP-GLU-GLY-LEU-HIS-CYS-URL-RLR-LEU-LYS-THR-RLR-RSN-150	GAG ATG	-019	<b>4</b>
		LEU-	<b>A</b>	HE HE		URL-(	[144]
	3TC (	JAL-1	<b>A</b>	886 LYS-	L JEJ	ſŸB−	<b>↓</b>
	ret (	-SYS-	<b>A</b>	LEU-	וכנ	SER-	<b>A</b>
	СВ	EB- (	<b>A</b>	3CG (	C THO	HIS-	4
	C 9 J	RO- S	<b>A</b>	3TG (	CCA CAT TCC TAC 6T6	-0Hc	4
	RGT CCG TCR TGT GTC CTT	70 SER-P	1	16T (		118 BSP-F	<b>A</b>
		7 HE-S	<b>A</b>	CTG CAC TGT 98 LEU-HIS-CYS	CGG GAT	1 186- f	<b>A</b>
	RTR TTC	LE- P	<b>A</b>	TG C EU-H		ISN-F	<b>A</b>
nC112	CAT A	IS- I		66T C C C C C C C C C C C C C C C C C C	CCC ART	RO- A	<b>Å</b>
-		ER- H	<b>1</b>	9 - N 19 .	ם מכנ	R0-P	4
	rg tet	AL-SI	<b>T</b>	6AC 6 ASP-6	RTT C	LE- P	*
	AR GTG	U- N	T A	6T GRC LY-RSP- L5E	AG	4S- 1	7
	1T GI	- C	<b>⊤</b>	16T 60	Н	.n- r:	$\mathbf{A}^{T}$
	T AAT	30-AS	<b>T</b>	TGC TC	RTC TTR	E- LE	
	וכ ככד	60 BLA-ASP-GLU-HIS-PRO-ASN-G	<b>T</b>		CAG A	Z Z	T
	GCR GAT GAR CAC	Э .U- HI	<b>↑</b>	RGT GGC 88 SER-GLY-	ATG CI	100 MET-G	Y ro
	T 68	69 P-611	<b>T</b>	T 867	T	R-7 Σ	- L35
	.a GA	A-AS	<b>A</b>	CGC TGT ARG-CYS-	ATC ACT	E- TH	<b>↑</b>
	39		<b>A</b>	)	I IE	르	7

F16. 4J

THR-PHE-SER-GLN-ASP-VAL-LEU-CYS-GLU-CYS-ARG-PRO-ILE-LEU-GLU-THR-THR-LYS-ALA-GLU-CAC ACA TTC TCT CAG GAT GTA CTC TGC GAA TGC AGG CCT ATT CTG GAG ACG ACA ARG GCA GAA RGG RGG ARA RCC ARG GGG RAG RGG CAR RGC ARA RCC CCA CAG RCT GAG GAR CCC 138 pCN2 pCN2 **[144]** 128

ARG-ARG-LYS-THR-LYS-GLY-LYS-ARG-LYS-GLN-SER-LYS-THR-PRO-GLN-THR-GLU-GLU-PRO-HIS-

150

F16. 4K

CTG TGA

	911	18 - MET-LYS- LEU- PHE-THR- CYS-PHE-LEU- GLN-URL-LEU- ALR-GLY-LEU-
	999	- <del>4</del> 19
	CT	ALA-
	CTR	-N3
	) ) (	1-18
	9	= - -
	CA	<u> </u>
	911	- LEU-
	Щ	18 PHE-
<b>-</b> 7	TGC	-SAJ
7	ACT	THR-
	Щ	PHE
	CTG	LEU-
	RAG	-SAT
	ATG	MET-
		ALA-
	CTG	1 YET- LEU- ALA
	ATG	MET-
	787	ATG CTG GCC ATG ARG CTG TTC ACT TGC TTC TTG CAG GTC CTA GCT GGG TTG

28 RLA- URL-HIS- SER-GLN-GLY-RIA-LEU- SER-RIA-GLY-RSN-RSN-SER-THR-GLU-MET-GLU-URL-URL-URL-GCT GTR CRC TCC CRG GGG GCC CTG TCT GCT GGG RRC RRC TCR RCR GRR RTG GRR GTG GTG - pcu2.1 -

PRO-PHE-RSN-GLU-URL-TRP-GLY-ARG-SER-TYR-CYS-ARG-PRO-MET-GLU-LYS-LEU-URL-TYR-ILE-CCT TTC AAT GAA GTG TGG GGC CGC AGC TAC TGC CGG CCA ATG GAG AAG CTG GTG TAC ATT - pcu2.1 -

ALA-ASP-GLU-HIS-PRO-ASN-GLU-UAL-SER-HIS-ILE-PHE-SER-PRO-SER-CYS-UAL-LEU-LEU-SER-GCA GAT GAA CAC CCT AAT GAA GTG TCT CAT ATA TTC AGT CCG TCA TGT GTC CTT CTG pCU2.1

FIG. 41

ARG-CYS-SER-GLY-CYS-CYS-GLY-ASP-GLU-GLY-LEU-HIS-CYS-UAL-ALA-LEU-LYS-THR-ALA-ASN-GTG GCG CTR RRG RCR GCC RRC RGT GGC TGC TGT GGT GRC GRG GGT CTG CRC TGT pCU2.1

ILE- THR-MET-GLN-ILE-LEU- LYS- ILE-PRO-PRO-RSN-RRG-RSP-PRO-HIS-SER-TYR-URL-GLU-MET-RTG CAG ATC TTA ARG ATT CCC CCC ART CGG GAT CCA CAT TCC TAC GTG GAG ATG 118 pCU2.1 -ATC ACT

THR-PHE-SER-GLN-ASP-UAL-LEU-CYS-GLU-CYS-ARG-PRO-ILE-LEU-GLU-THR-THR-LYS-ALA-GLU-TCT CAG GAT GTA CTC TGC GAA TGC AGG CCT ATT CTG GAG ACG ACA ARG GCA GAA pCU2.1 ACA TTC

AGG TAR

138

ARG \*

-16. 4M

A RCC RTG RRC TTT CTG CTC TCT TGG GTG CRC TGG RCC CTG GCT TTR CTG CTG TRC CTC CRC CRT  18  MET-RSN-PHE-LEU-LEU-SER-TRP-URL-HIS-TRP-THR-LEU-RLR-LEU-LEU-LEU-TYR-LEU-HIS-HIS-  15-15	ILU-GLY-GLU-GLN-LYS-RIF	RRG TTC RTG GRC GTC TRC CRG CGC RGC TRT TGC CGT CCG RTT GRG RCC CTG GTG GRC RTC LVS- PHE-MET-RSP- URL- TVR- GLN- RRG- SER- TVR- CVS- RRG- PRO- ILE- GLU- THR- LEU- URL- RSP- ILE- L46
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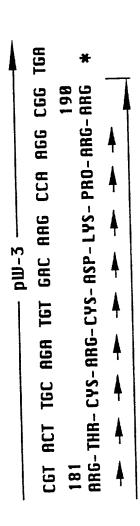
F16. 5

7E - 3H - 3	7C CRG 61 7HE-GLN- 7HE-GLN- 7HE-GLN- 81 81 81	6R6 6C6 8LA-	TC CRG GRG TRC CCC GRI  HE-GLN-GLU-TYR-PRO-RSI  GG TGT GCG GGC TGC TGC  81  RG-CYS-RLR-GLY-CYS-CY	PRO- CYS-	-ASP - TGC TGC - C4.S -	GRG ATA GLU- ILE- ASN-ASP	ATA - 1LE - ASP -	019 CELU-	GRG TRT RTC TTC RRG 78 GLU- ТҮR- ILE- РНЕ- L ЧS- GRR GCC CTG GRG TGC 90 GLU- RLR- LEU- GLU- СУS- 146	238 — L RTC — L46 — L46 — L46 — L46 — L46 — L59 = L46 — L59 = L59 = L46 — L58 = L58	11C	BAG LYS- CYS-	CCG GTG URL-	RRG CCG TCC - LYS-PRO- SER- ТGC GTG ССС - CYS- URL-PRO-	TGT GTG CYS- UAL.	TGT GTG CCC CYS- URL-PRO- RCG TCG GRG THR-SER-GLU-	CCC CTR -PRO-LEU GRG RGC	HGC - SER-	T GAG ATA GAG TAT ATC TTC AAG CCG TCC TGT GTG CCC CTA ATG  P-GLU-ILE-GLU-TYR-ILE-PHE-LYS-PRO-SER-CYS-UAL-PRO-LEU-MET-  C AAT GAT GAA GCC CTG GAG TGC GTG CCC ACG TCG GAG AGC AAC  S-ASN-ASP-GLU-ALA-LEU-GLU-CYS-UAL-PRO-THR-SER-GLU-SER-ASN-A538  L46  188	
6TC 101 URL-	GTC ACT 181 URL-THR-	ATG MET-	CAG -GLN-	ATC - 11.E-	ATG MET	CGG - ARG-	ATC - ILE-	ABAR - LYS.	RAR CCT CAC CAR 110 LYS-PRO-HIS-GLN-	CAC HIS-	CAA GLN-	AGC - Ser-	CAG	CAC - HIS-	ATA - ILE-	66A . 6LY	GGA GAG ATG GLY-GLU-MET-	RTG -MET	GTC ACT ATG CAG ATC ATG CGG ATC AAA CCT CAC CAA AGC CAG CAC ATA GGA GAG ATG AGC 120 120 110 1110 1110 1110 1110 1110 11	1
									. 146											i

FIG. 5A

TTC CTG CRG CRT RGC RGR TGT GRA TGC RGR CCR RRG RRG GRT RGR RCR RRG CCR GRR RRT 150 121 PHE-LEU-GLN-HIS-SER-RRG-CVS-GLU-CVS-RRG-PRO-LVS-LVS-RSP-RRG-THR-LVS-PRO-GLU-RSN-L20	CAC TGT GRG CCT TGT TCR GRG CGG RGR RRG CRT TTG TTT GTC CRR GRT CCG CRG RCG TGT 158  141  HIS-CYS-GLU-PRO-CYS-SER-GLU-RRG-RRG-LYS-HIS-LEU-PHE-URL-GLN-RSP-PRO-GLN-THR-CYS-	RRR TGT TCC TGC RRR RRC RCR GRC TCG CGT TGC RRG GCG RGG CRG CTT GRG TTR RRC GRR 189 161 LYS- CYS-SER-CYS-LYS-RSN-THR-RSP-SER-RRG-CYS-LYS-RLR-RRG-GLN-LEU-GLU-LEU-RSN-GLU-LS9 128
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FIG. 5B



F16. 5C

	<b>—</b>	ATG AAG CTG TTC ACT TGC TTC TTG CAG GTC CTA GCT GGG TTG		MET-LYS-LEU- PHE-THR-CYS-PHE-LEU-GLN-UAL-LEU-ALA-GLY-LEU-
CU2 ·		GCT		ALB-
pcu2		CTA		LEU-
		GTC		· URL-
İ		CAG		- N 15
		TTG		LEU-
		110	18	-PHE-
	- 21	<b>16</b> C		-CAS-
	- 282	ACT		-THR-
		πc		- PHE
		CTG		- LEU-
		AAG		-LYS-
				MET
		229		. ALA.
		RTG CTG		AET- LEU- ALA-
	Ì	<b>R</b> TG		MET

	GTG	ALR-LEU- SER-FILR-GLY-RSN-RSN-RSN-SER- THR-GLU-MET-GLU-URL-URL-URL-LIR-LEU- SER-FILR-GLU-MET-GLU-URL-URL-LIR-LIR-LEU- SER-FILR-GLU-MET-GLU-URL-URL-LIR-LIR-LIR-LIR-LIR-LIR-LIR-LIR-LIR-L
	919	<b>ਛ</b> ↓ ↓
	GRA	
	BTG (	THE A
	BH	V-SER- THR- GLU- MET- GLU- URL- URI V- V- V
	CB (	
	CA A	E 7 7 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
	AC T	38 RSN-S
	<b>E</b>	
	AB	SE ↑ ↑
	999	BLA-614- ASN
DCU2	GCT	, <del>E</del> <b>A</b> , <b>A</b>
	GCC CTG TCT GCT GGG ARC ARC TCA ACA GAA ATG GAA GTG GTG	RICH-LEU- SER-FICH-GLY-RSN
	CTG	≟ੈੈ
	229	· 是 4 . 4 ¥
	CAG	- 2 2
	בככ	SER-
	CAC TCC CAG 666	28 HIS-
	GTA	20 ALA- VAL- HIS- SER- GLN- GLY
	GCT GTA	ALA-

40 PRO- PHE- ASN- GLU- UAL- TRP- GLY- ARG- SER- TYR- CYS- ARG-PRO- MET- GLU- LYS- LEU- UAL- TYR- ILE-CCT TTC ART GRA GTG TGG GGC CGC RGC TRC TGC CGG CCR RTG GRG RRG CTG GTG TRC RTT pCU2 - [144]

F1G. 6

GRA GTG TCT CAT ATA TTC AGT CCG TCA TGT GTC CTT CTG AGT  70  GLU- UAL-SER- HIS- ILE- PHE- SER- PRO- SER- CYS- UAL- LEU- LEU- SER-	GGT GRC GRG GGT CTG CRC TGT GTG GCG CTR RRG RCR GCC RRC  98  GLY-RSP-GLU-GLY-LEU-HIS-CYS-URL-RLR-LEU-LYS-THR-RLR-RSN-	ANG ATT CCC CCC RAT CGG GAT CCA CAT TCC TAC GTG GAG ATG  118  LYS- ILE- PRO- PRO- RSN- ARG- ASP- PRO- HIS- SER- TYR- UAL- GLU- MET-
70 70 - SEF	161 - 169 98 - 299	GR] 116
10000000000000000000000000000000000000	CAC - HIS	CGG
HH HH - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -		HRIT HSN.
CGT CRT	pcV2 GGT GLY-	pCUZ CCC
TCT SER-	CRG	
GTG UAL-	GAC ASP-	150 HTT HTT-
-N 19		ABBG LYS-
HRIT -NSR	T6T CYS-	HEU-
CCT PB0-	TGC CYS-	F = -
CBC HIS-	-419 299	
GCA GAT GAA CAC CCT AAT 60 ALA-ASP-GLU-HIS-PRO-ASN-	CGC TGT AGT GGC TGC TGT 80 ARG-CYS-SER-GLY-CYS-CYS-	RTC RCT RTG CRG RTC TTR 180 ILE- THR- MET-GLN- ILE- LEU-
GAT ASP-	T6T CYS-	量 量
GCA BLA-	CGC ARG-	ATC ILE-

FIG. 6A

135

	CTC TGC GAR TGC RGG CCT ATT CTG GRG RCG RCR RRG GCR GRR	1139 and	LEU- CYS- GLU- CYS-AKG-PKU-ILE- LEU- ULU- INN- INN- LTS- NLN- OLU-	<b>A A</b>
	π cr6 6	58	Lt- LEU-1	
	CCT ATT	138	- PRU-ILE-	
— pcu2 —	TGC AGG		CYS-HKU	
	GAR	;	- CT N-	— [L44]
	TGC		) -	
			t	
	GTA		- URL	
	GRT		- ASP	<b>A</b>
	CAG		SIN.	4
	TCT	128	-SER-	<b>A</b>
	ACA TTC TCT CAG GAT GTA		THR- PHE-SER- GLN-ASP-UAL	<b>4 4 4 4</b>
	BC		H	4

ARG-ARG-LYS-THR-LYS-GLY-LYS-ARG-LYS-GLN-SER-LYS-THR-PRO-GLN-THR-GLU-GLU-GLU-PRO-HIS-RGG RGG RAR ACC RRG GGG RRG RGG RRG CAR RGC RAR ACC CCR CRG RCT GRG GRA CCC CAC - pcu2 -

CTG TGA

158 LEU F16. 6B

		911	18 1ET-LYS- LEU- PHE-THR- CYS-PHE-LEU- GLN-DÄL-LEU- ALA-GLY-LEU-
_		999	-61.Y-
pCU2.1		GCT	ALA-
		CTA	LEU-
		GTC	UAL-
V		TG AAG CTG TTC ACT TGC TTG CAG GTC CTA GCT 666 TTG	-N 15
		1Т6	LEU-
		πc	18 PHE-
	7	<b>1</b> 9C	CYS-
	- 202	ACT	THR-
		Щ	PHE-
		CTG	LEU-
		AAG	LYS-
		ATG	MET-
		229	ALA-
		CTG	1 MET- LEU- ALA- MI
	1	ATG CTG GCC AT	— MET-

ALA- UAL-HIS- SER-GLN-GLY-FILA-LEU- SER-FILA-GLY-ASN-ASN-ASN-SER- THR-GLU-MET-GLU-UAL-UAL-GCT GTA CAC TCC CAG GGG GCC CTG TCT GCT GGG AAC AAC TCA ACA GAA ATG GAA GTG - pcu2.1 -

PRO~ PHE- ASN- GLU- UAL- TRP- GLY- ARG- SER- TYR- CYS- ARG- PRO- MET- GLU- LYS- LEU- UAL- TYR- ILE-H CCT TTC AAT GAA GTG TGG GGC CGC AGC TAC TGC CGG CCA ATG GAG AAG CTG GTG TAC - pcu2.1 -

ALA-ASP-GLU-HIS-PRO-ASN-GLU-UAL-SER-HIS-ILE-PHE-SER-PRO-SER-CYS-UAL-LEU-LEU-SER-CAT ATA TTC AGT CCG TCA TGT GTC CTT CTG AGT pCU2.1 -GCA GAT GAA CAC CCT AAT GAA GTG TCT

ARG-CYS-SER-GLY-CYS-CYS-GLY-ASP-GLU-GLY-LEU-HIS-CYS-UAL-ALA-LEU-LYS-THR-ALA-ASN-GGT CTG CAC TGT GTG GCG CTA ARG ACA GCC AAC pcU2.1 -RGT GGC TGC TGT GGT GRC GRG CGC TGT

ILE- THR- MET-GLN- ILE- LEU- LYS- ILE- PRO- PRO- ASN- ARG- ASP- PRO- HIS- SER- TYR- URL- GLU- MET-CCC ART CGG GAT CCA CAT TCC TAC GTG GAG ATG 118 pCU2.1 ATC ACT ATG CAG ATC TTA AAG ATT CCC

THR- PHE-SER- GLN-ASP-VAL-LEU-CYS-GLU-CYS-ARG-PRO-ILE-LEU-GLU-THR-THR-LYS-ALA-GLU-TCT CAG GAT GTA CTC TGC GAA TGC AGG CCT ATT CTG GAG ACG ACA ARG GCA GAA pCU2.1 -128 **ACA TTC** 

AGG TAR

ARG 138

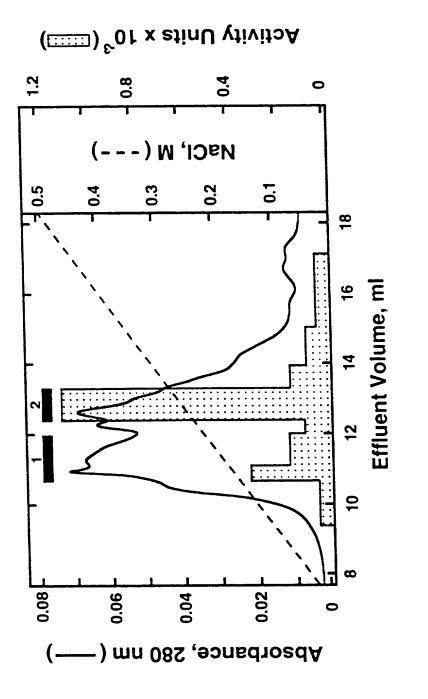
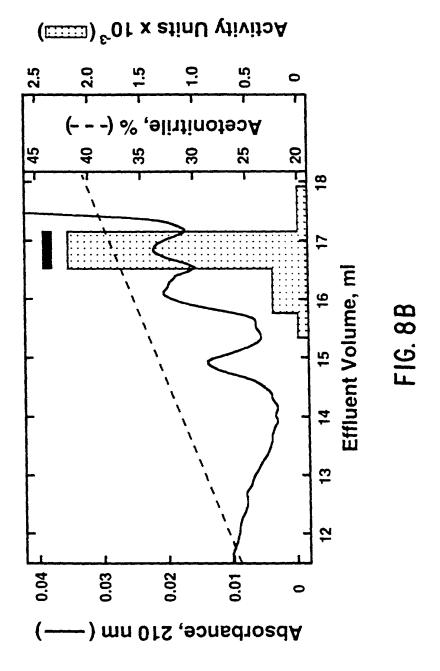


FIG. 8A

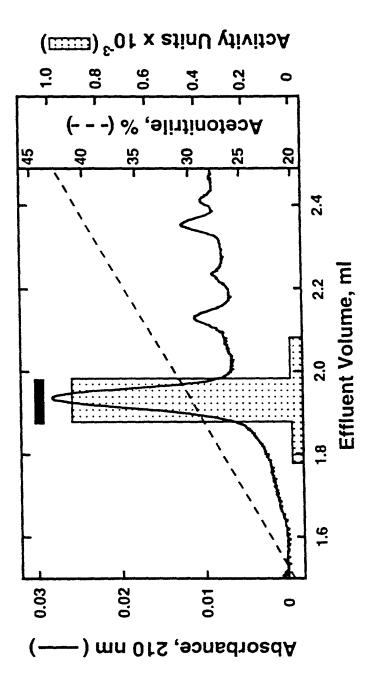


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F16.8C

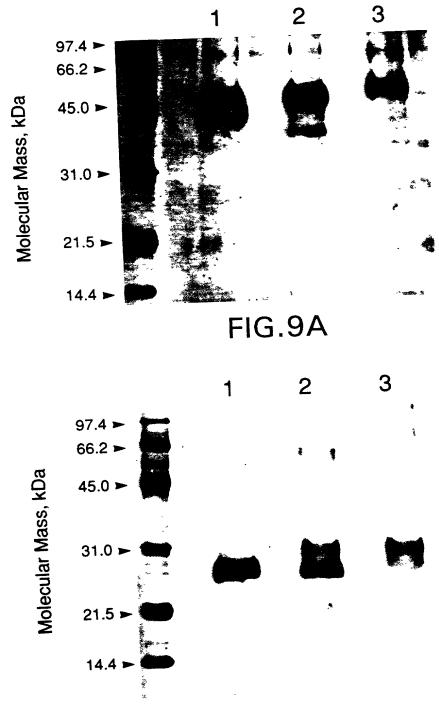


FIG.9B

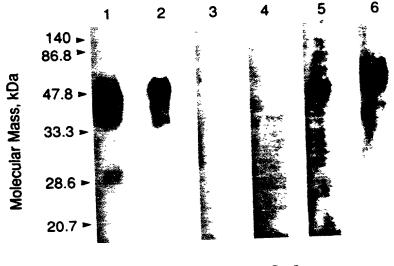


FIG.10A

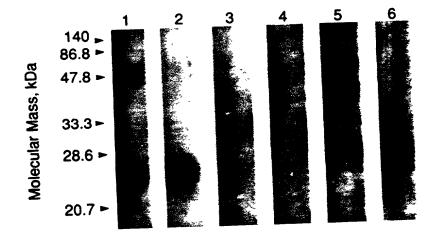
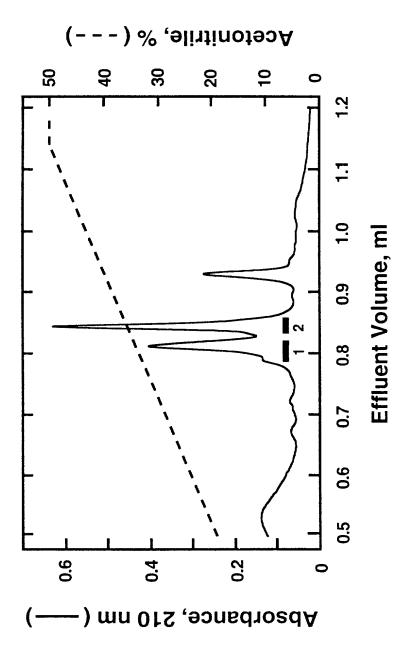


FIG.10B

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F16. 11